14. (As Filed) The method of claim 1, further comprising administering an antiviral agent to the patient.

15. (As Filed) The method of claim 1, further comprising administering an antiinflammatory agent to the patient.

16. (As Filed) The method of claim 1, wherein the agent is formulated with a carrier as a pharmaceutical composition.

17. (As Filed) The method of claim 1, wherein the patient is a pediatric patient.

REMARKS

Status of the Invention.

Claims 1-17 are pending and stand rejected in the application. With entry of this amendment, claims 1 and 13 have been amended. Claim 1 has been amended to correct a typographic error. Claim 1 has also been amended to recite that patients contemplated for treatment with the claimed methods do not have multiple sclerosis, and has support, e.g., on page 18, lines 13-14. Claim 13 has been amended for improved clarity and has support, e.g., on page 9, lines 20-24. No new matter has been introduced by the claim amendments.

Claim amendments are for purposes of improved clarity or consistency of claim language unless otherwise noted, and should not be construed as an acquiescence in any ground of rejection. Issues raised by the Examiner in the Office Action are addressed below with reference to the paragraph numbering of the Office Action.

2. & 3. The typographic error noted by the Examiner has been corrected. Further, "HSV-1" was inadvertently spelled as "HIV-1" on page 17, line 26. The error has also been corrected. The other requirements noted by the Examiner, e.g., sequence listing and trademark designation, have been complied with in the specification as filed.

5. Rejection of claims 3, 20-23 under 35 U.S.C. 112, first paragraph

Claims 1-8, 11, and 14-17 have been rejected for the alleged lack of enablement. First, while acknowledging enablement with respect to antibodies directed to the α4 subunit of VLA-4, the Examiner states that the specification does not enable the use of

other agents that inhibit leukocyte binding to endothelial cells in the treatment of encephalitis. In addition, the Examiner is of the opinion that there is a lack of correlation between animal model studies and in vivo clinical trial results, and that the claimed methods are unpredictable in the absence of in vivo clinical data. This rejection is respectfully traversed for the reasons stated below.

(a) Methods for screening binding agents for use in the claimed methods are enabled

The Examiner is of the view that the subject specification has not provided sufficient information (e.g., molecular weight, amino acid composition) that distinctly identifies agents which inhibit leukocytes binding to endothelial cells. The Examiner says that there is insufficient direction or objective evidence as to how to make and use such agents. This assertion is respectfully traversed.

First, besides antibodies, other specific examples of binding agents that inhibit VLA-4 binding to VCAM-1 are also discussed in the specification. For example, the specification discloses peptides that have a binding affinity for VLA-4 with an IC50 of 50 μM or less (page 9, lines 25 to page 10, line 6). According to the disclosure, the peptides have the formula (R1-Y/F-G/E-R2)n or R-PVSF-R' (II). R and R' are sequences of 0-7 amino acid totaling not more than 9 amino acids. R1 is a sequence of 0-6 amino acids and R2 is a sequence of 1-7 amino acids, totaling not more than 2-11 amino acids. N is 1 or 2. Optionally 1 amino acid is a D-amino acid and the N terminus is optionally modified by attachment of R4-CO- or R5-O. The C terminus is optionally modified by replacement of OH by NR7R8 or O-R6; R4 = H, lower alkyl, cycloalkyl, aryl or aralkyl. R5 is as R4 but not H. R6 is as R5. R7 and R8 are as R4. Other peptides, peptide derivatives or cyclic peptides that bind to VLA-4 and block its binding to VCAM-1 are described in references which were incorporated by reference in the subject specification (page 10, lines 6-10).

In addition, it must be noted that although agents which specifically inhibit leukocytes binding to endothelial cells (VCAM-1 binding to the α4 subunit of VLA-4) may be structurally diverse, the subject specification has provided extensive teachings as to how to obtain such binding agents by producing and screening large combinatorial libraries (see, e.g., page 15, line 14 to page 16, line 4). At the priority date of the subject application, there were

several techniques available which would enable synthesis and screening of large combinatorial libraries. For example, the specification discloses that combinatorial libraries can be produced for many types of compound that can be synthesized in a step-by-step fashion. Such compounds include polypeptides, beta-turn mimetic, polysaccharides, phospholipids, hormones, prostaglandins, steroids, aromatic compounds, heterocyclic compounds, benzodiazepines, oligomeric N-substituted glycines and oligocarbamates. The specification also teaches that large combinatorial libraries of the compounds can be constructed by the encoded synthetic libraries (ESL) method (as discussed in WO 95/12608, WO 93/06121, WO 94/08051, WO 95/35503, and WO 95/30642). In addition, at the priority date of the subject application, peptide libraries could also be generated by phage display methods (see, e.g., WO 91/18980).

The specification further discloses that the libraries of compounds can be initially screened for specific binding to the alpha-4 integrin subunit of VLA-4 or to VCAM-1, optionally in competition with a reference compound known to have blocking activity. Appropriate activity can then be confirmed using one of the assays described in the specification (pages 8-9).

Screening a library of candidate agents for the claimed methods is feasible because the activity demanded of the agents for use in the claimed methods is not a complex biological activity, but rather a simple binding activity. That is, the desired class of agents is defined by capacity to bind to an epitope of VLA-4 involved in VCAM-1 binding or vice versa. For example, in the phage display method noted above, the libraries are contacted with a target and screened by affinity selection for binding to the target. In the present situation, the target would be VCAM-1 or VLA-4 and the phage library would be screened for binding to one of these targets, optionally in competition with VLA-4 or VCAM-1, respectively. The phage display method has been widely used by the skilled persons to isolate polypeptide ligands to a variety of targets.

In view of the foregoing, it is respectfully submitted that the subject specification and knowledge well known in the relevant art at the priority date of the subject application would have enabled one of skill in the art to screen binding agents that inhibit leukocytes binding to endothelial cells.

(b) Results from the in vivo animal model studies correlate with and enable the claimed methods

In maintaining the rejection for alleged lack of enablement, the Examiner also questions the correlation between animal model studies and in vivo clinical results, and states that it is not clear results from the animal models accurately reflect the relative efficacy of any agent in treating viral encephalitis in humans. The Examiner states that adhesion-based therapy encounters inherent difficulties and are unpredictable in the absence of in vivo clinical data. Applicants respectfully traverse.

The legal standard for judging whether disclosed data is sufficient to satisfy the enablement requirement of 35 U.S.C. 112, first paragraph, is whether there is *a reasonable correlation* between the evidence and the asserted utility (see MPEP 2107.02, citing *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985; *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980)). According to the MPEP, "[t]he applicant *does not have to prove* that a correlation exists between a particular activity and an asserted therapeutic use of a compound *as a matter of statistical certainty*, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted" (MPEP 2107.02-I; emphasis added). The MPEP reiterates that "as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use." (MPEP 2107.02-I).

With respect to clinical data, it is well settled that the legal standard for patentability and the assessment of success by the medical community are not the same, and that the PTO ought to apply the legal standard, not the medical standard, to the examination of patent applications. In *In re Brana,* 34 USPQ2d 1436, 1441 (Fed. Cir. 1995), the Federal Circuit stated the PTO had "confuse[d] the requirements under the law for obtaining a patent with the requirements under the law for marketing a particular drug for human consumption," and supported its position with the following quote from an earlier case: "[t]esting for the full safety and *effectiveness* of a prosthetic device is more properly left to the Food and Drug Administration." *Brana,* 34 USPQ2d 1436, 1442 (emphasis added). The Court added that: "[t]he stage at which an invention in this field [pharmaceutical inventions] becomes useful is well *before* it is ready to be administered to humans." *Id.* (emphasis added).

Consistent with this legal standard, the MPEP expressly states that:

> Office personnel *should not impose on applicants the unnecessary burden of providing evidence from human clinical trials*. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) [MPEP 2107.02-IV; emphasis added].

In the subject application, Applicants have disclosed that treatment with α4 integrin antibody is effective in preventing or ameliorating immune-mediated CNS damage following viral encephalitis in rats. The effects include a reduction in prevalence and severity of clinical Borna disease, a reduction in body weight loss, and a reduction in the severity of encephalitis. The experimental results further indicate that the treatment blocks the immunopathological immune response to viral encephalitis without causing enhanced viral replication (see Examples, pages 23-28). Thus, the subject application has demonstrated that the monoclonal α4 integrin antibody is effective in treating viral encephalitis in rats. One of skill in the art could reasonably conclude that such in vivo animal testing results would correlate with treatment of human viral encephalitis as claimed in the subject invention, which is all that is required to satisfy the enablement requirement. The law does not require Applicants to provide clinical data to support the claimed methods.

In light of the above remarks, it is respectfully submitted that the claimed methods of treatment are enabling. Accordingly, withdrawal of the rejection is respectfully requested.

6. The Examiner questions whether the 21.6 antibody has been deposited in a manner that 35 U.S.C. 112, first paragraph is satisfied. In response, the Examiner is advised that the subject specification has provided the amino acid sequences of the variable regions of the humanized 21.6 antibody (SEQ ID Nos. 1 and 2). Such sequences are all that is required in order for a skilled artisan to obtain a humanized 21.6 antibody or any desired isotype using

routine techniques well known in the art. No undue experimentation is required. Further, the detailed procedures to construct the humanized 21.6 antibody along with its amino acid sequences were disclosed with great detail in WO 95/19790 (Athena Neurosciences), which was incorporated by reference in the subject specification (page 9, lines 18-21, and page 28, lines 7-10).

7. Rejection of claim 13 under 35 U.S.C. 112, second paragraph.

Claim 13 has been amended to delete the recitation of "21.6" and to clarify that the recited amino acid sequences relate to the humanized antibody. Therefore, the alleged indefiniteness has been eliminated. Accordingly, withdrawal of the rejection is respectfully requested.

10. The Examiner cites Bendig et al. (U.S. Patent No. 5,840,299) in rejecting claims 1-13 and 15-16 under 35 U.S.C. 102(e). The Examiner states that Bendig et al. teaches the use of VLA-α4-specific antibodies to treat multiple sclerosis and encephalitis. The Examiner also cites Soilu-Hanninen et al. (Archives of Neurology 53: 125-133, 1996; hereinafter "Soilu-Hanninen 1996a") and Soilu-Hanninen et al. (J. Neuroimmunol. 72:95-105, 1997; hereinafter "Soilu-Hanninen 1997") which allegedly reported that herpes virus is present in more multiple sclerosis patients than control cases and that viral infections serve as triggers of relapse release phases of multiple sclerosis. The Examiner then states that Bendig et al. differs from the claimed methods only by not disclosing a viral source of encephalitis, but that the functional limitations of the claimed methods would have been inherent properties of treating multiple sclerosis patients with VLA-α4-specific antibodies.

Claim 1 has been amended to recite that patients to be treated with the claimed methods are limited to those that are free of multiple sclerosis. As explained below, such amendment further distinguishes the claimed methods over the cited art.

Bendig et al. relates to the use of VLA-α4-specific antibodies in the treatment of inflammatory responses of CNS, especially multiple sclerosis. Soilu-Hanninen 1996a merely reports that HSV was present in more multiple sclerosis cases than control ones. Specifically, it reports that 46% of multiple sclerosis cases and 28% control cases have HSV-1 or HSV-2

infections. However, neither reference proposes treating herpes virus infected patients that are free of multiple sclerosis.

As to Soilu-Hanninen 1997, it discusses treatment of virus-facilitated EAE with VLA-4-specific mAb. Unlike the claimed methods, it does not discuss treatment of patients with herpes viral infection but free of multiple sclerosis. In Soilu-Hanninen 1997, the virus which induced the EAE was Semliki Forest virus, not herpes virus as claimed in the subject invention. Further, as discussed in the specification, EAE is a syndrome that simulates multiple sclerosis in humans and is different from viral induced simple encephalitis (page 18, lines 9-12). Unlike simple viral encephalitis, which is caused by an inflammatory response to viral infection, multiple sclerosis is a complex autoimmune syndrome, probably of multifactorial origin. In this regard, it should be noted that the subject specification specifically discloses that the present methods are generally not employed on EAE animals, or on humans suffering from multiple sclerosis (page 18, lines 13-14).

In light of the above remarks and amendments, Applicants respectfully request that the rejection under 35 U.S.C. 102(e) over Bendig et al. be withdrawn.

11. & 12. Claims 1, 2, 4, 6-9 and 16 have been rejected under 35 U.S.C. 102(b) as being anticipated by Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996; hereinafter "Soilu-Hanninen et al. 1996b") and Soilu-Hanninen 1997. In maintaining the rejection, the Examiner states that the Soilu-Hanninen et al. references teach treatment of virus-facilitated EAE using VLA-α4-specific antibodies.

It is to be noted that Soilu-Hanninen 1996b is essentially an abstract of Soilu-Hanninen 1997 discussed above. Therefore, the above discussions of Soilu-Hanninen 1997 are equally applicable to both of the references cited by the Examiner in maintaining the instant rejection. In view of the discussions and claim amendment noted above, it is submitted that the claimed methods are novel over the cited art, and that the instant rejection should be withdrawn.

13. Claims 1-17 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bendig et al. in view of Soilu-Hanninen 1996b and/or Soilu-Hanninen 1997. The Examiner is of the view that Bendig et al. differs from the claimed methods by not disclosing a

viral source of encephalitis, and that the two Soilu-Hanninen et al. references suggest the correlation between multiple sclerosis and viral infection. Therefore, the Examiner states that one of skill in the art would have been motivated to select VLA-α4-specific antibodies to treat viral encephalitis. This assertion is respectfully traversed for the reasons stated below.

The presently claimed methods are directed to treating viral encephalitis by blocking adhesion of T lymphocytes with brain endothelial cells. As discussed in the specification, inflammation (e.g., due to undesired T lymphocyte response) plays a complex role in viral encephalitis as demonstrated by results obtained from studies of Borna disease virus (BDV) (page 4, lines 12 to page 5, line 5). BDV causes a severe T-lymphocyte mediated encephalitic response in the brain, and Borna disease is mainly due to the immune response to BDV antigens, rather than direct effects of BDV damage to the brain. It has been found that activated, BDV-antigen specific, T-lymphocytes also express α4 integrin. However, T cells specific for Borna disease virus can both prevent and augment Borna disease depending on the stage of infection. The T cells are protective if they are administered to an experimental animal before infection. On the other hand, if the T cells are administered after infection, they augment symptoms of the disease (page 4, lines 28 to page 5, line 5). Due to such a complex role of inflammation in viral encephalitis, it would have been unpredictable, prior to the subject invention, at which therapeutic target attempts to abort inflammation (e.g., blocking the binding of α4-integrin on T cells to VCAM-1 on brain endothelial cells) should best be directed, and whether such attempts would ameliorate or exacerbate this disease. Facing such uncertainties, a skilled artisan would not have been motivated by Bendig et al. and Soilu-Hanninen et al. in treating viral encephalitis as specified in the present claims.

In addition, as noted above, the pending claims have been amended to recite treatment of viral encephalitis patients that are free of multiple sclerosis. On the other hand, all of the cited references relate to either treatment of multiple sclerosis or EAE, which is distinguished from simple viral encephalitis.

In view of the foregoing, it is submitted that the claimed invention is nonobvious over the cited art. Withdrawal of the rejection is respectfully requested.

14. Claims 1-17 have also been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over the art cited in paragraph 13 in further view of Planz et al. (J. Virol. 69: 896-903, 1995).

The Examiner states that Planz et al. teaches the role of T lymphocyte subsets in the induction of progressive encephalitis by Borna disease virus. The Examiner is of the opinion that such teachings, in conjunction with the teachings of the other cited art, render the claimed methods *prima facie* obvious.

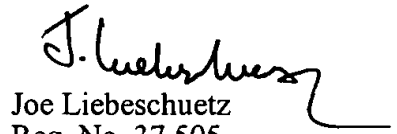
It is acknowledged that Planz et al. discusses the roles of different subsets of T cells in borne disease virus-induced progressive encephalitis. However, there is no discussion in Planz et al. regarding treatment of encephalitis with anti-adhesion agents such as anti-VLA-4 antibodies. Thus, the above remarks regarding the nonobviousness of the claimed methods are equally applicable to the instant rejection. Therefore, it is respectfully submitted that the claimed methods are also nonobvious over the art cited by the Examiner in maintaining the instant rejection. Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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